

WHAT IS CLAIMED IS:

1. A system for inducible expression of a chimeric antigen receptor comprising:
 - a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a polynucleotide coding for a chimeric antigen receptor comprising a ligand binding domain, wherein the ligand binding domain is specific for a ligand, wherein the ligand is a tumor specific molecule, viral molecule, or any other molecule expressed on a target cell population, wherein the ligand can elicit recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and d) a polynucleotide coding for an intracellular signaling domain; and
 - b) a second nucleic acid comprising a second promoter operably linked to nucleic acid coding for a transcriptional activator for the inducible promoter.
2. The system of claim 1, wherein the drug is tamoxifen and/or its metabolites.
3. The system of claim 2, wherein the first promoter comprises a nucleic acid sequence of SEQ ID NO: 41.
4. The system of any one of claims 1-3, wherein the second promoter is a constitutive promoter.
5. The system of claim 4, wherein the second promoter is the EF1 α p.
6. The system of any one of claims 1-5, wherein the transcriptional activator comprises a sequence of SEQ ID NO: 40.
7. The system of any one of claims 1-6, wherein the first nucleic acid further comprises a first vector and the second nucleic acid further comprises a second vector.
8. The system of claim 7, wherein both vectors are packaged in a viral vector.
9. The system of claim 8, wherein the viral vector is a lentivirus.

10. The system of any one of claims 1-6, wherein the first and second nucleic acid comprise a vector.
11. The system of any one of claims 1-10, wherein the first nucleic acid further comprises a nucleic acid sequence coding for a selectable marker.
12. The system of anyone of claims 1-11, wherein the second nucleic acid further comprises a nucleic acid coding for a selectable marker.
13. A system for inducible expression of chimeric antigen receptor comprising:
 - a) a first nucleic acid comprising a first promoter inducible by a drug, wherein the first nucleic acid is operably linked to a polynucleotide coding for a cytokine, a chemokine receptor, a polypeptide that regulates apoptosis, or a polypeptide that modulates checkpoint signaling; and
 - b) a second nucleic acid comprising a second promoter operably linked to nucleic acid coding for a transcriptional activator for the inducible promoter.
14. The system of any one of claims 1-13, wherein the second nucleic acid further comprises a polynucleotide coding for chimeric antigen receptor comprising a ligand binding domain, wherein the ligand is a tumor specific molecule, viral molecule, or any other molecule expressed on a target cell population, wherein the ligand can elicit recognition, modulation, inhibition, and/or elimination by a lymphocyte; a polynucleotide coding for a polypeptide spacer, wherein the spacer is optimized; a polynucleotide coding for a transmembrane domain; and d) a polynucleotide coding for an intracellular signaling domain.
15. The system of any one of claims 1-14 wherein the first promoter is in opposite orientation to the second promoter.
16. The system of any one of claims 1-15, wherein the ligand binding domain is an antibody fragment.

17. The system of claim 16, wherein the ligand binding domain is single chain variable fragment.
18. The system of any one of claim 1-17, wherein the tumor specific molecule is selected from the group consisting of CD19, CD20, CD22, CD23, CD123, CS-1, ROR1, CE7, EGFR, hB7H3, mesothelin, c-Met, PSMA, Her2, GD-2, MAGE A3 TCR and combinations thereof.
19. A chimeric receptor polypeptide coded for by the first second and/or second nucleic acid of the system of any one of claims 1-18 or 34-38.
20. A host cell comprising a system of any one of claims 1-18 or 34-38.
21. The host cell of claim 20, wherein the host cell is a CD8+ T cytotoxic lymphocyte cell selected from the group consisting of naïve CD8+ T cells, central memory CD8+ T cells, effector memory CD8+ T cells and bulk CD8+ T cells.
22. The host cell according to claim 21, wherein the host cell is a CD4+ T helper lymphocyte cell that is selected from the group consisting of naïve CD4+ T cells, central memory CD4+ T cells, effector memory CD4+ T cells, and bulk CD4+ T cells.
23. A composition comprising a host cell of any one of claims 20-22 or 39-40, in a pharmaceutically acceptable excipient.
24. The composition of claim 23 comprising a host cell of claim 21 and a host cell of claim 22.
25. An *in vitro* method for preparing a host cell of any one of claims 20-22 or 39-40 comprising:
- a) providing a system of any one of claims 1-18 or 34-38; and
 - b) introducing the system into a separate isolated T lymphocyte population and expanding each T lymphocyte population in vitro.

26. The method of claim 25, wherein the T lymphocytes are expanded, and wherein the method further comprises culturing the cells in the presence of anti-CD3 and/or anti CD28, and at least one homeostatic cytokine until the cells expand sufficiently for use as a cell infusion.
27. The method of any one of claims 25 or 26, wherein the lymphocyte is CD8+ or CD4+.
28. A use of the host cell of any one of claims 20-22 or 39-40 or the composition of claims 23-24 or 41 in combination with a drug that induces expression of a transgene in the host cell or composition for the treatment of cancer or a viral infection.
29. The use of claim 28, wherein the cancer is a solid tumor or hematologic malignancy.
30. The use of claim 29, wherein the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer.
31. A method of performing cellular immunotherapy in a subject having cancer or a viral infection comprising: administering the composition of any one of claims 23 to 24 or a host cell of any one of claims 20-22 or 39-40 to the subject and administering a drug that induces expression of a transgene in the composition or the host cells.
32. The method of claim 31, wherein the cancer is selected from a solid tumor or hematologic malignancy.
33. The method of claim 32, wherein the solid tumor is selected from the group consisting of a breast cancer, brain cancer, lung cancer, colon cancer, renal cancer, pancreatic cancer, prostate cancer, and ovarian cancer.
34. The system of any one of claims 1-3 or 4-12 wherein the second promoter is an inducible promoter.

35. The system of any one of claim 1-12 or 34, wherein the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor.

36. The system of any one of claims 13-18, wherein the second promoter is an inducible promoter.

37. The system of any one of claims 13-18, wherein the second promoter is constitutive promoter.

38. The system of any one of claims 14-18 or 36-37, wherein the spacer is optimized for increased T cell proliferation and/or cytokine production in response to the ligand as compared to a reference chimeric receptor.

39. The host cell of claim 20, wherein the host cell is a precursor T cell.

40. The host cell of claim 39, wherein the precursor T cell is a hematopoietic stem cell.

41. The composition of claim 23 comprising a host cell of claim 21 or 22 and a host cell of claim 39 or 40.

42. The method of claim 25 or 26, wherein the isolated T lymphocyte population comprises precursor T cells.

43. The method of claim 42, wherein the precursor T cells are hematopoietic stem cells.

44. The method of claim 31, wherein the administering of the drug is performed with the administering the composition or host cells.

45. The method of claim 31, wherein the administering of the drug is performed after administering of the composition or host cells, wherein administering is performed 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 2 weeks, 4 weeks or two months, or any time in between any two values of time listed.

CLAIMS

1. A system for inducible expression of a polynucleotide comprising:
 - (a) a first nucleic acid comprising a first promoter which comprises the nucleotide sequence set forth in SEQ ID NO:41, wherein the first nucleic acid is operably linked to a polynucleotide;
 - (b) a second nucleic acid comprising a second promoter operably linked to a nucleic acid encoding a transcriptional activator for the first promoter; and
 - (c) an agent selected from the group consisting of tamoxifen, a metabolite of tamoxifen, and an analog of tamoxifen.
2. The system of claim 1, further comprising: (d) an activating stimulator selected from the group consisting of an anti-CD3 antibody, an anti-CD28 antibody, and an antigen binding fragment thereof.
3. The system of claim 1, wherein the agent is selected from 4-hydroxytamoxifen or 4-hydroxy-N-desmethyltamoxifen.
4. The system of claim 1, wherein the second promoter is a constitutive promoter.
5. The system of claim 4, wherein the second promoter is an EF1 α promoter.
6. The system of claim 1, wherein the transcriptional activator comprises a 4-hydroxytamoxifen (4-OHT)-dependent transcriptional regulator (HEA-3) polypeptide.
7. The system of claim 1, wherein the transcriptional activator comprises the amino acid sequence set forth in SEQ ID NO:40.
8. The system of claim 1, wherein a first vector comprises the first nucleic acid, and a second vector comprises the second nucleic acid.
9. The system of claim 8, wherein the first vector and the second vector are packaged in a viral vector.
10. The system of claim 9, wherein the viral vector comprises a lentiviral vector.
11. The system of claim 1, wherein the first nucleic acid or the second nucleic acid further comprises a nucleotide sequence encoding a selectable marker.
12. The system of claim 1, wherein the first promoter is in an opposite orientation to the second promoter.

13. The system of claim 1, wherein the polypeptide comprises a cytokine, a chemokine receptor, or a chimeric antigen receptor (CAR), wherein the CAR comprises a ligand binding domain, a spacer, a transmembrane domain, and an intracellular signaling domain.

14. The system of any one of claims 1-13, further comprising an *ex vivo* host cell comprising the first nucleic acid and the second nucleic acid.

15. The system of claim 14, wherein the host cell is a T cell.

16. The system of claim 14, wherein the host cell is selected from the group consisting of a CD4⁺ T cell, a CD8⁺ T cell, a precursor T cell, and a hematopoietic stem cell.

17. The system of claim 14, wherein the host cell is a CD8⁺ cytotoxic T lymphocyte cell selected from the group consisting of a naïve CD8⁺ T cell, a central memory CD8⁺ T cell, an effector memory CD8⁺ T cell, and a bulk CD8⁺ T cell.

18. The system of claim 14, wherein the host cell is a CD4⁺ helper T lymphocyte cell selected from the group consisting of a naïve CD4⁺ T cell, a central memory CD4⁺ T cell, an effector memory CD4⁺ T cell, and a bulk CD4⁺ T cell.

19. A pharmaceutical composition for use in the treatment of a cancer or a viral infection, comprising the system of claim 14, and a pharmaceutically acceptable excipient.

20. The pharmaceutical composition of claim 19, wherein the cancer comprises a solid tumor.

21. The pharmaceutical composition of claim 19, wherein the cancer is a breast cancer, a brain cancer, a lung cancer, a colon cancer, a renal cancer, a pancreatic cancer, a prostate cancer, an ovarian cancer, or a hematologic malignancy.

22. An *in vitro* method for preparing a population of cells for infusion, the method comprising:

(a) providing the system of any one of claims 1-13;

(b) introducing the first nucleic acid and the second nucleic acid into an isolated T cell population; and

(c) culturing the T cell population in the presence of the agent.

23. The method of claim 22, wherein (c) further comprises culturing the T cell population in the presence of an activating stimulator selected from the group consisting of an anti-CD3 antibody, an anti-CD28 antibody, and an antigen binding fragment thereof.

24. The method of claim 22, wherein the T cell population comprises a cell selected from the group consisting of a CD4⁺ T cell, a CD8⁺ T cell, a precursor T cell, and a hematopoietic stem cell.

25. The method of claim 24, wherein the cell is a CD8⁺ cytotoxic T lymphocyte cell selected from the group consisting of a naïve CD8⁺ T cell, a central memory CD8⁺ T cell, an effector memory CD8⁺ T cell, and a bulk CD8⁺ T cell; or wherein the cell is a CD4⁺ helper T lymphocyte cell selected from the group consisting of a naïve CD4⁺ T cell, a central memory CD4⁺ T cell, an effector memory CD4⁺ T cell, and a bulk CD4⁺ T cell..